

REVIEW AND META-ANALYSIS

Metabolic Syndrome and Risk of Incident Cardiovascular Events and Death

A Systematic Review and Meta-Analysis of Longitudinal Studies

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Objectives

The purpose of this research was to assess the association between the metabolic syndrome (MetSyn) and cardiovascular events and mortality by meta-analyses of longitudinal studies.

Background

Controversy exists regarding the cardiovascular risk associated with MetSyn.

Methods

We searched electronic reference databases through March 2005, studies that referenced Reaven's seminal article, abstracts presented at meetings in 2003 to 2004, and queried experts. Two reviewers independently assessed eligibility. Longitudinal studies reporting associations between MetSyn and cardiovascular events or mortality were eligible. Two reviewers independently used a standardized form to collect data from published reports. Authors were contacted. Study quality was assessed by the control of selection, detection, and attrition biases.

Results

We found 37 eligible studies that included 43 cohorts (inception 1971 to 1997) and 172,573 individuals. Random effects meta-analyses showed MetSyn had a relative risk (RR) of cardiovascular events and death of 1.78 (95% confidence interval [CI] 1.58 to 2.00). The association was stronger in women (RR 2.63 vs. 1.98, $p = 0.09$), in studies enrolling lower risk ($<10\%$) individuals (RR 1.96 vs. 1.43, $p = 0.04$), and in studies using factor analysis or the World Health Organization definition (RR 2.68 and 2.06 vs. 1.67 for National Cholesterol Education Program definition and 1.35 for other definitions; $p = 0.005$). The association remained after adjusting for traditional cardiovascular risk factors (RR 1.54, 95% CI 1.32 to 1.79).

Conclusions

The best available evidence suggests that people with MetSyn are at increased risk of cardiovascular events. These results can help clinicians counsel patients to consider lifestyle interventions, and should fuel research of other preventive interventions. (J Am Coll Cardiol 2007;49:403-14) © 2007 by the American College of Cardiology Foundation

The metabolic syndrome (MetSyn), also termed the insulin resistance syndrome, is the concurrence in an individual of multiple metabolic abnormalities associated with cardiovascular disease. Cross-sectional surveys indicate that, in the U.S., one-third of adults (1) and an alarming proportion of children (2) have the MetSyn. It represents a global public health problem (3,4). Since 1988, when Reaven (5) first systematically described it, an abundance of research has advanced an understanding of the pathophysiology, epidemiology, prognostic implications, and therapeutic strategies

related to the MetSyn. Despite this progress, fundamental uncertainties persist regarding the MetSyn, as highlighted by recent national and international diabetes organizations' doubt regarding even its existence (6).

Reaven's (5) first definition of the MetSyn included these components: hyperglycemia, abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol concentration, and hypertension. Its pathogenesis, unified by the putative mechanism of insulin resistance, was thought to be related to interactions between sedentary lifestyle, diet, and genetic factors. In 1998, the American Diabetes Association proposed that MetSyn is comprised of glucose intolerance, central obesity, dyslipidemia (including increased triglycerides, decreased high-density lipoprotein cholesterol concentration, and increased small dense low-density lipoprotein cholesterol concentration), hypertension, increased prothrombotic and antifibrinolytic factors, and risk for atherosclerotic disease; but, it did not propose

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Abbreviations and Acronyms

CI = confidence interval
MetSyn = metabolic syndrome
NCEP = National Cholesterol Education Program
RR = relative risk
WHO = World Health Organization

specific definitions or thresholds for these processes (7). In 1999, the World Health Organization (WHO) codified specific components and thresholds for the MetSyn (8), and in 2003 the U.S. National Cholesterol Education Program (NCEP) redefined the MetSyn in an attempt to simplify the clinical application of its criteria and improve its recognition (9). Despite these efforts, there exists no gen-

uine consensus of the unique components that comprise the MetSyn (4,10). Burgeoning information regarding its pathophysiology adds to the uncertainty (11).

Only recently have there been studies assessing the risk of incident cardiovascular disease events attributable to the MetSyn. These studies had different populations, definitions of MetSyn, methods, and results. Because of this variability and the current controversy regarding its implications (6), we propose that a systematic review and meta-analysis of the existing data will provide the current best evidence. In addition to providing an overall estimate of risk, the tools of meta-analysis allow an evaluation of differences between studies that could clarify the prognostic implications of how MetSyn is defined, in which settings it may be informative, and other issues related to its clinical use (12,13).

We performed a meta-analysis of longitudinal studies that assessed any cardiovascular event outcomes or mortality in people with clustering of 3 or more coronary risk factors (regardless of whether this was termed the MetSyn) compared with people without that phenotype. We expected to capitalize on the high heterogeneity between studies to identify likely explanations for it in factors related to population characteristics, outcome and exposure ascertainment, and study quality. The reporting of this systematic review follows current standards (14).

Methods

Study eligibility. Eligible studies: 1) were randomized trials or cohort studies; 2) reported a risk estimate (or frequency data from which one could be calculated) for MetSyn, its synonyms, or clustering of 3 or more coronary risk factors; and 3) reported a single or combined cardiovascular event outcome or mortality. There were no exclusion criteria or language restrictions.

Search strategy. A content expert and a master's level medical librarian with extensive meta-analytical experience collaborated to design the search strategies. We searched the following electronic databases on March 1, 2005: Ovid MEDLINE (from 1966), Ovid EMBASE (from 1988), Web of Science (from 1993), and Cochrane Library (from inception). Our search of Web of Science included a match

between terms for cardiovascular outcomes and publications that cited Reaven's article (5). Figure 1 shows the strategy for MEDLINE (the other strategies are available from the authors).

We hand-searched conference proceedings from the 2003 and 2004 annual scientific sessions of the European Society of Cardiology, American Heart Association, American College of Cardiology, and American Diabetes Association for relevant abstracts to identify full peer-reviewed publications not yet indexed. We queried experts of endocrinology and cardiology, and we reviewed bibliographies of retrieved publications to further increase our yield of potentially relevant articles.

Study selection. Using a high threshold for exclusion, one investigator examined all abstracts and selected articles for full text examination. Two investigators independently used piloted, standardized forms to assess the eligibility of all full text articles. We collaborated with translation services to examine articles in languages other than English. We assessed interobserver agreement by the phi and kappa statistics (15,16), and we resolved differences by consensus.

Data collection. Two investigators independently used piloted, standardized forms to abstract data from included studies and other publications reporting their methods. We contacted original study authors in order to obtain missing data.

For each study, we recorded the year of cohort inception, the setting (community subjects vs. medical patients), participant characteristics related to the MetSyn, and the number of participants with prevalent coronary heart disease and diabetes mellitus. Exposure data collected included the definitions and criteria for MetSyn and its components, the number of participants with and without MetSyn for each definition, and the duration of follow-up. Outcome data collected included the definitions of cardiovascular outcomes, the numbers of participants with and without MetSyn who did and did not have the outcome(s), the multivariable adjusted risk estimate (relative risk [RR], hazard ratio, or odds ratio) for MetSyn and for different numbers of its components for each outcome, and the variables incorporated into the multivariable analyses. When a study reported only risk estimates for different numbers of MetSyn components, rather than a risk estimate for MetSyn or 3 or more components, we used the risk estimate for 3 components to reflect that of the MetSyn (an approach that would underestimate the risk).

Quality assessment. We measured the quality, or internal validity, of studies by assessing their control of selection bias, detection bias, and attrition bias (17). For control of selection bias, we assessed if multivariable risk estimates incorporated age, gender, smoking, and coronary heart disease history, when applicable. For control of detection bias, we assessed if the outcome assessors were unaware (either explicitly or de facto due to temporal relationships) of subjects' MetSyn status. For control of attrition bias, we assessed the extent of loss to follow-up.

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Cardiovascular disease*exp
OR
Mortality*exp
OR
Text words: Cardiovascular, coronary artery disease, stroke,
myocardial infarction, cardiac, heart, death, mortality, fatal

AND

Metabolic syndrome
OR
Syndrome X
OR
Insulin resistance syndrome
OR
Elevated blood pressure*exp AND lipid disorder*exp
OR
Elevated blood pressure*exp AND obesity*exp
OR
Elevated blood pressure*exp AND elevated blood glucose*exp
OR
Elevated blood pressure*exp AND proteinuria*exp
OR
Lipids disorder*exp AND obesity*exp
OR
Lipid disorder*exp AND elevated blood glucose*exp
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Lipid disorder*exp AND proteinuria*exp
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Obesity*exp AND elevated blood glucose*exp
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Figure 1 Literature Search Strategy Used for the MEDLINE Database

Loss to follow-up is traditionally represented as a proportion of the total initial study population, but this approach does not provide sufficient information about how loss to follow-up in a study affects the reliability of its risk estimate. In this study, we describe attrition bias by the ratio of the number of subjects lost to follow-up to the number of outcome events in the study (loss-events ratio). This is a direct measure of how influential loss to follow-up could be for a risk estimate in a given study, and we arbitrarily considered a loss-events ratio <10% as satisfactory control of attrition bias.

Statistical analysis. The results of each cohort study were reported as an RR, hazard ratio, odds ratio, or dichotomous frequency data. We treated hazard ratios as RRs. Because event rates were not sufficiently low in some high-risk study populations, we did not assume that odds ratios were comparable to RRs. We algebraically converted odds ratios and frequency data into RRs. When available, we used the adjusted risk estimates from multivariate models.

We performed separate meta-analyses with the DerSimonian and Laird (18) random effects model to obtain the pooled RR for each outcome and the pooled RR for the primary end point of *incident cardiovascular events and death*.

For the latter, when studies reported multiple outcomes, we incorporated them into subsequent analyses based on the following hierarchical list of outcomes (from broader to more specific cardiovascular outcomes, followed by all-cause mortality): cardiovascular events, coronary heart disease events, cardiovascular death, coronary heart disease death, and all-cause death. Similarly, when studies reported results based on multiple MetSyn criteria, we incorporated them based on the following hierarchical list of criteria: NCEP, modified NCEP, WHO, modified WHO, and other criteria. We used the Cochran's Q test to assess between-study differences and the I^2 statistic to quantify the proportion of observed inconsistency across study results not explained by chance (19). We proposed pre-defined subgroup analyses to test the effect of methodology and participant characteristics on the strength of association. Heterogeneity between subgroups was calculated with Cochran's Q test (20), and comparisons of risk estimates between subgroups were made with a test of interaction (21).

Using the same methods, we performed an additional meta-analysis of studies that reported a risk estimate for MetSyn that was adjusted in multivariable models for any or all of the components that make up the syndrome. This analysis aimed to quantify the additive cardiovascular risk

attributable to the MetSyn above that which is conferred by its component risk factors.

The presence of publication bias was investigated graphically by the method of Sterne and Egger (22), and its implications for our results were assessed by the fail-safe *n* (23) and the trim-and-fill method (24).

All analyses were performed with Comprehensive Meta Analysis Version 2 (Biostat, Englewood, New Jersey) (25).

Data Synthesis

Search results and study inclusion. Our initial search identified 4,198 unique publications, which were narrowed by preliminary review to 104 potentially relevant original articles. The search of conference proceedings and query of experts did not identify additional articles. Sixty-seven articles were excluded (some for multiple reasons) because of cross-sectional study design (*n* = 10), lack of measurement or report of outcome data for MetSyn, its synonyms, or clustering of 3 or more coronary risk factors (*n* = 61), or lack of measurement of cardiovascular events or death (*n* = 2). There were 37 eligible reports (interobserver raw agreement 96%, $\phi = 0.93$, $\kappa = 0.91$). One article that studied the same cohort as another included article was excluded (26), and 1 article presented results for 2 independent studies (27). In another study, the investigators performed 11 cohort studies (by applying modified MetSyn criteria to existing baseline subject data from 11 prior epidemiologic studies that assessed mortality during long-term follow-up) and reported a pooled result for 7 of those cohorts (28). Ultimately, our meta-analysis included 36 reports that described 37 studies including 43 unique cohorts (Fig. 2) (27–62).

Qualitative summary. Table 1 summarizes the characteristics of the included studies. They were all published since 1998, included cohorts with inception between 1971 and 1997, and had follow-up from 2.2 to 18.8 years. Sample sizes ranged from 133 to 41,056 participants (total 172,537), and there was a wide range of prevalence of cardiovascular disease and diabetes mellitus at inception.

The MetSyn was defined by WHO criteria in 6 studies (36,41,47,48,51,61), NCEP criteria in 12 studies (39,40,42,43,47,53–55,57,59,61,62), modified WHO criteria in 4 studies (28,39,54,58), and modified NCEP criteria in 10 studies (27,39,44–46,49,50,56,60). Most modifications substituted body mass index for waist circumference or waist-to-hip ratio, or omitted the proteinuria component of the WHO criteria. A few studies added additional components, such as C-reactive protein (45) and uric acid (38,52). Factor analysis was used in 5 studies (31,33,34,39,52) to create a novel variable, or factor, comprised of statistical loadings of highly inter-correlated participant characteristics (analogous to clustered risk factors in the MetSyn), which was then used as a parameter in regression models for incident cardiovascular disease. The factors in these studies were nearly identical to the components in WHO and NCEP definitions of MetSyn. Some studies developed MetSyn criteria using threshold values for its components based on the extreme tertiles to quintiles of their distribution (30,32,35,37). One study that presumably had a predominantly Japanese population used a lower threshold for systemic obesity (a body mass index >25 kg/m²) in its modified WHO criteria (58), but no other studies modified their criteria to account for ethnic differences.

Eleven studies assessed cardiovascular events (which in some studies included cardiovascular death), 18 studies

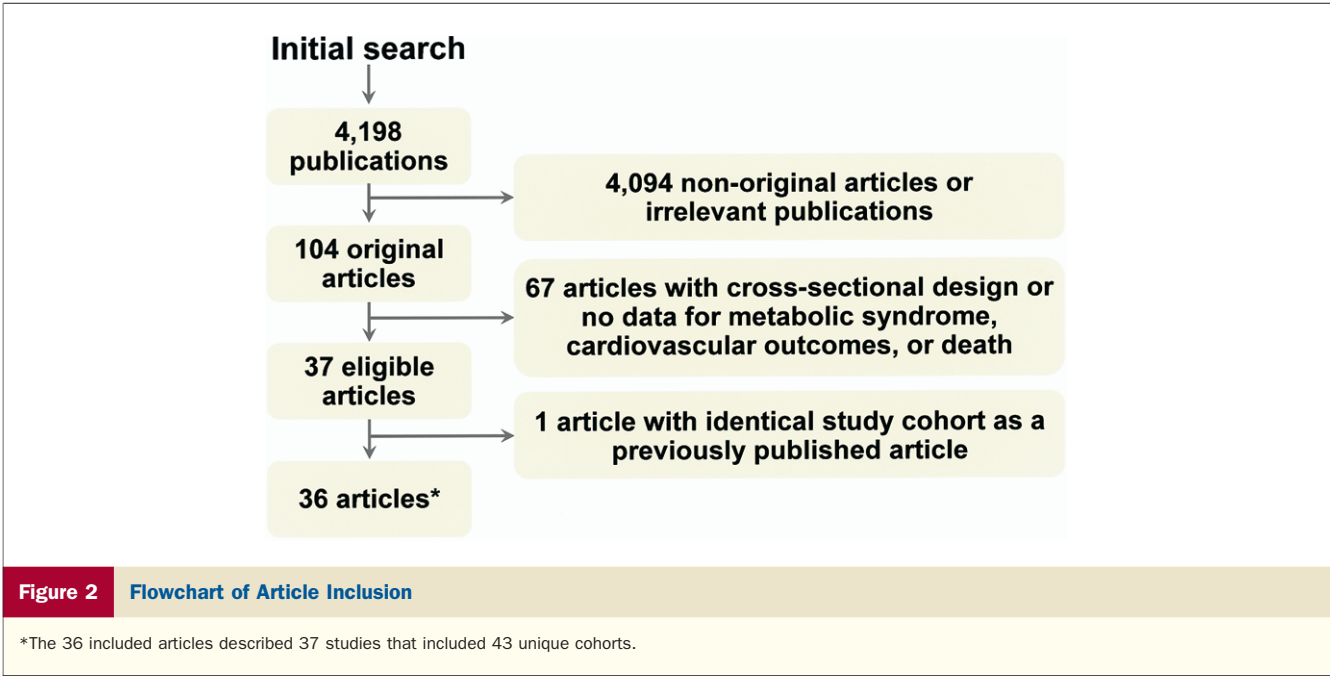


Table 1 Characteristics of Cohort Studies of Metabolic Syndrome and Incident Cardiovascular Disease and Death

Study Author, Year	Cohort Inception Year	Follow-Up, yrs	Setting	Sample Size, n	Mean Age, yrs	Men, %	CVD, %	DM, %	MS Criteria	MS, %	Outcomes	Controlled Selection Bias	Controlled Attrition Bias
Anderson et al., 2004 (46)	1994	2.8	M	2,035	65	76	100	30	Modified NCEP	66	CHD events	✓	✓
Bonora et al., 2003 (a) (41)	1990	5.0	C	888	59	51	10	23	WHO NCEP	34 18	CHD events	✓	
Bonora et al., 2004 (b) (47)	1988	4.3	M	559	63	45	0	100	WHO	91	CV events	✓	
Bruno et al., 2004 (48)	1991	8.2	M	1,565	69	43	24	100	WHO	76	Death CV death	✓	✓
Corsetti et al., 2004 (49)	1994	2.2	M	766	58	77	100	0	Modified NCEP	36	CHD events		✓
Ford, 2004 (50)	1976	13.5	C	2,431	50	46	18	3	Modified NCEP	26	Death CV death CHD death	✓	X
Gimeno Orna et al., 2004 (51)	1994	4.6	M	318	65	41	21	100	WHO	77	CV events CHD events		✓
Girman et al., 2004 (a) (27)	1988	5.4	M	1,991	59	81	100	0	Modified NCEP	21	CHD events		✓
Girman et al., 2004 (b) (27)	1986	5.0	C	3,188	58	85	0	0	Modified NCEP	46	CHD events		✓
Godsland et al., 2004 (52)	1971	10.6	C	649	47	100	0	0	Factor analysis	NA	CHD events		
Holvöet et al., 2004 (53)	1997	5.0	C	3,033	74	48	13	19	NCEP	38	CHD events	✓	✓
Hsia et al., 2003 (42)	1997	2.8	M	294	65	0	100	37	NCEP	60	CHD death CV events CHD events		
Hu et al., 2004 (28)	NA	8.5	C	9,522	56	46	X	0	Modified WHO	15	Death CV death		✓
Hunt et al., 2004 (54)	1984	12.7	C	2,815	43	43	7	11	NCEP Modified WHO	25 25	Death CV death		
Isomaa et al., 2001 (36)	1990	6.9	M	4,483	54	48	6	38	WHO	46	Death CV death	✓	
Katzmarzyk et al., 2004 (55)	1979	10.2	M	19,223	43	100	0	<1	NCEP	20	Death CV death	✓	✓
Kaukua et al., 2001 (37)	1979	10.0	M	133	56	53	32	100	Other	54	Death CV death		✓
Klein et al., 2002 (38)	1988	4.8	C	2,957	62	43	0	0	Other	19	CV events		
Lakka et al., 2002 (39)	1984	11.6	C	1,209	52	100	0	0	NCEP Modified NCEP Modified WHO-1 Modified WHO-2 Factor analysis	9 14 14 13 NA	Death CV death CHD death	✓	✓
Lehto et al., 2000 (33)	1982	7.2	M	902	58	55	15	100	Factor analysis	NA	CHD death		✓
Lempianin et al., 1999 (31)	1986	7.0	C	1,069	69	37	20	0	Factor analysis	NA	CHD events	X	✓
Malik et al., 2004 (56)	1976	13.0	C	6,255	50	46	27	13	Modified NCEP	27	Death CV death CHD death	✓	✓
Marroquin et al., 2004 (57)	1996	3.5	M	755	58	0	38	32	NCEP	57	Death CV events	✓	
McNeill et al., 2005 (62)	1987	11.0	C	12,089	54	43	0	0	NCEP	23	CHD events	✓	✓

Continued on next page

Table 1 Continued

Study Author, Year	Cohort Inception Year	Follow-Up, yrs	Setting	Sample Size, n	Mean Age, yrs	Men, %	CVD, %	DM, %	MS Criteria	MS, %	Outcomes	Controlled Selection Bias	Controlled Attrition Bias
Nakanishi et al., 2004 (58)	1994	7.0	C	6,182	48	100	0	7	Modified WHO	7	CV events	✓	
Onat et al., 2002 (40)	1997	3.0	C	2,398	49	50	8	6	NCEP	33	CHD events		✓
Pyörälä et al., 2000 (34)	1971	18.8	C	970	48	100	0	0	Factor analysis	NA	CV events CHD events	✓	✓ ✓
Resnick et al., 2003 (43)	1989	7.6	C	2,283	55	43	0	0	NCEP	35	CV events	✓	✓
Ridker et al., 2003 (44)	1992	10.1	C	14,719	54	0	0	0	Modified NCEP	24	CV events CHD events		
Rutter et al., 2004 (59)	1991	6.9	C	3,037	54	45	0	0	NCEP	24	CV events		✓
Sattar et al., 2003 (45)	1989	4.9	C	6,447	55	100	0	0	Modified NCEP	26	CHD events	✓	✓
Schillaci, 2004 (60)	1988	4.1	M	1,742	50	55	0	6	Modified NCEP	34	CV events CHD events	✓	✓
Sprecher et al., 2000 (35)	1987	8.2	M	6,428	62	81	100	20	Other	12	Death		✓
Stern et al., 2004 (61)	1984	7–8	C	2,570	X	X	0	X	WHO NCEP	X 36	CV events	✓	
Tenkanen et al., 1994 (29)	1981	5.0	C	2,035	47	100	0	3	Other	X	CHD events	✓	✓
Trevisan et al., 1998 (30)	1978	7.0	C	4,056	47	55	X		Other	15	Death CV death CHD death		
Wilson et al., 1999 (32)	1971	16.0	C	3,577	X	49	0	X	Other	19	CHD death CHD events		

Data are for subjects included in analyses of incident cardiovascular disease (CVD) or death, and may differ from the characteristics of the total study populations. Definitions for metabolic syndrome, outcomes, and biases are in the Methods section.

C = community; CHD = coronary heart disease; CV = cardiovascular; DM = diabetes mellitus; M = medical; MS = metabolic syndrome; NA = not applicable; NCEP = National Cholesterol Education Program; WHO = World Health Association; X = unknown.

assessed coronary heart disease events (which in some studies included coronary heart disease death), 10 studies assessed cardiovascular deaths, 7 studies assessed coronary heart disease death, and 12 studies assessed all-cause death (Table 1, outcomes). The loss-events ratio ranged from 0% to 990%, and in 23 studies it was less than 10% (Table 1, attrition bias). Age, gender, smoking, and prevalent cardiovascular disease were simultaneously controlled for, when necessary, in half of the studies (Table 1, selection bias). Not shown in the table, detection bias was controlled for in all studies. Selection, detection, and attrition biases were concomitantly limited in 12 studies (29,34,39,43,45,46,48,53,55,56,60,62).

Meta-analyses. Separate meta-analyses for each outcome (cardiovascular events, coronary heart disease events, cardiovascular death, coronary heart disease death, and all-cause death) demonstrated that the magnitude of risk for the different outcomes assessed in the studies was similar (Fig. 3). This supported our strategy for subsequent analyses to pool the risk estimates for studies reporting different outcomes based on the hierarchies described earlier. The overall pooled RR for incident cardiovascular events and death for people with the MetSyn was 1.78 (95% confidence interval [CI] 1.58 to 2.00) (Fig. 4).

In the 7 studies that provided separate risk estimates for both genders, the risk of incident cardiovascular events and death was higher for women compared with men (RR 2.63 vs. 1.98, $p = 0.09$). Other within-study subgroups were not analyzed, because the studies only rarely reported risk estimates for subgroups other than gender.

Significant heterogeneity existed between studies ($I^2 = 82\%$), and we conducted the planned between-study subgroup analyses to investigate its sources. The RR of cardiovascular events and death was significantly different between the WHO criteria, NCEP criteria, factor analysis, and other criteria (2.06 vs. 1.67 vs. 2.68 vs. 1.35, $p = 0.005$).

Variability between studies that used “other” definitions were due to chance ($I^2 = 0\%$), as was nearly all of the variability between studies that used factor analysis ($I^2 = 4\%$); however, there were still large inconsistencies between studies using WHO and NCEP criteria (both $I^2 > 75\%$). This heterogeneity was not explained by use of different obesity metrics (body mass index vs. waist circumference or waist-to-hip ratio vs. either) ($p = 0.7$).

We compared subgroups and studies that included only diabetic patients with those that excluded diabetic patients (RR 1.51 vs. 1.69), those that included only coronary heart disease patients to those that excluded coronary heart disease patients (RR 2.68 vs. 1.94), and studies that included community subjects with those that included medical patients (RR 1.69 vs. 1.70), but these comparisons did not explain the heterogeneity between studies (all $p > 0.10$). The background risk of the study populations (as determined by the event rate in the subjects without MetSyn) was a significant source of heterogeneity ($p = 0.047$), and MetSyn posed a greater risk in populations with background event rates $< 10\%$ compared with populations with background event rates $> 10\%$ (RR 1.96 vs. 1.43, $p = 0.04$). Attrition bias ($p = 0.02$) but not selection bias ($p = 0.4$) contributed to heterogeneity. Studies with high attrition ($\geq 10\%$ loss-events ratio) had a significantly higher risk of cardiovascular events and death than those with low attrition (RR 2.31 vs. 1.63, $p = 0.001$).

Figure 5 shows the results of the meta-analysis of studies that simultaneously adjusted for MetSyn and its components. The pooled results showed an increased risk of cardiovascular disease or death in patients with MetSyn, even after controlling for its component risk factors (RR 1.54, 95% CI 1.32 to 1.79). The results of the studies were homogeneous ($p = 0.23$); furthermore, the observed inconsistency ($I^2 = 32\%$) suggested that most of the variability between these studies was due to chance.

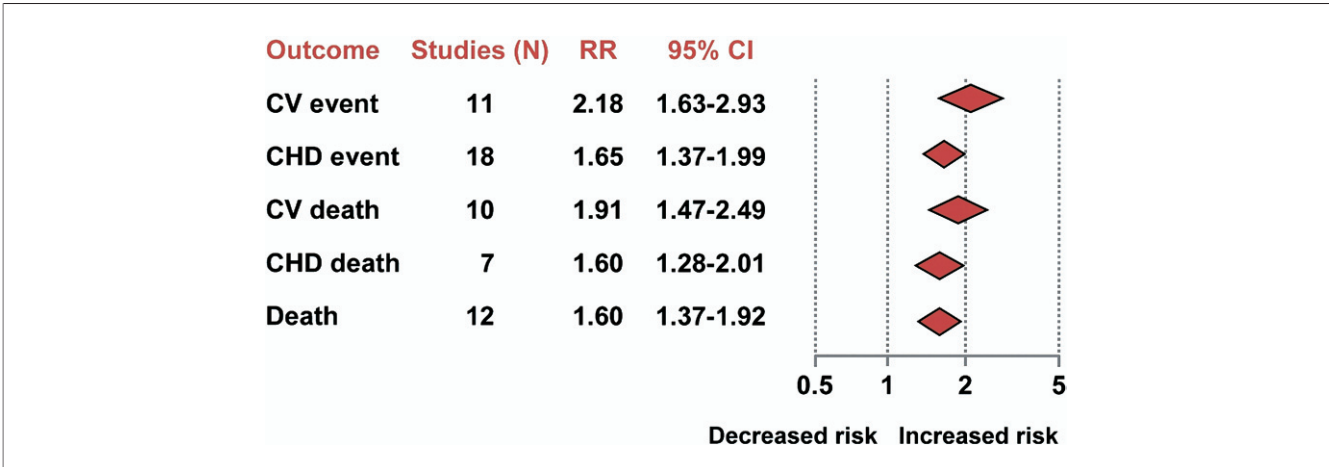


Figure 3 RR and 95% CI for Metabolic Syndrome and Incident Cardiovascular Events and Death, by Specific Outcomes

The diamonds represent the pooled relative risk (RR) and 95% confidence interval (CI) for studies that assessed each outcome. Some studies assessed more than 1 outcome. CHD = coronary heart disease; CV = cardiovascular.

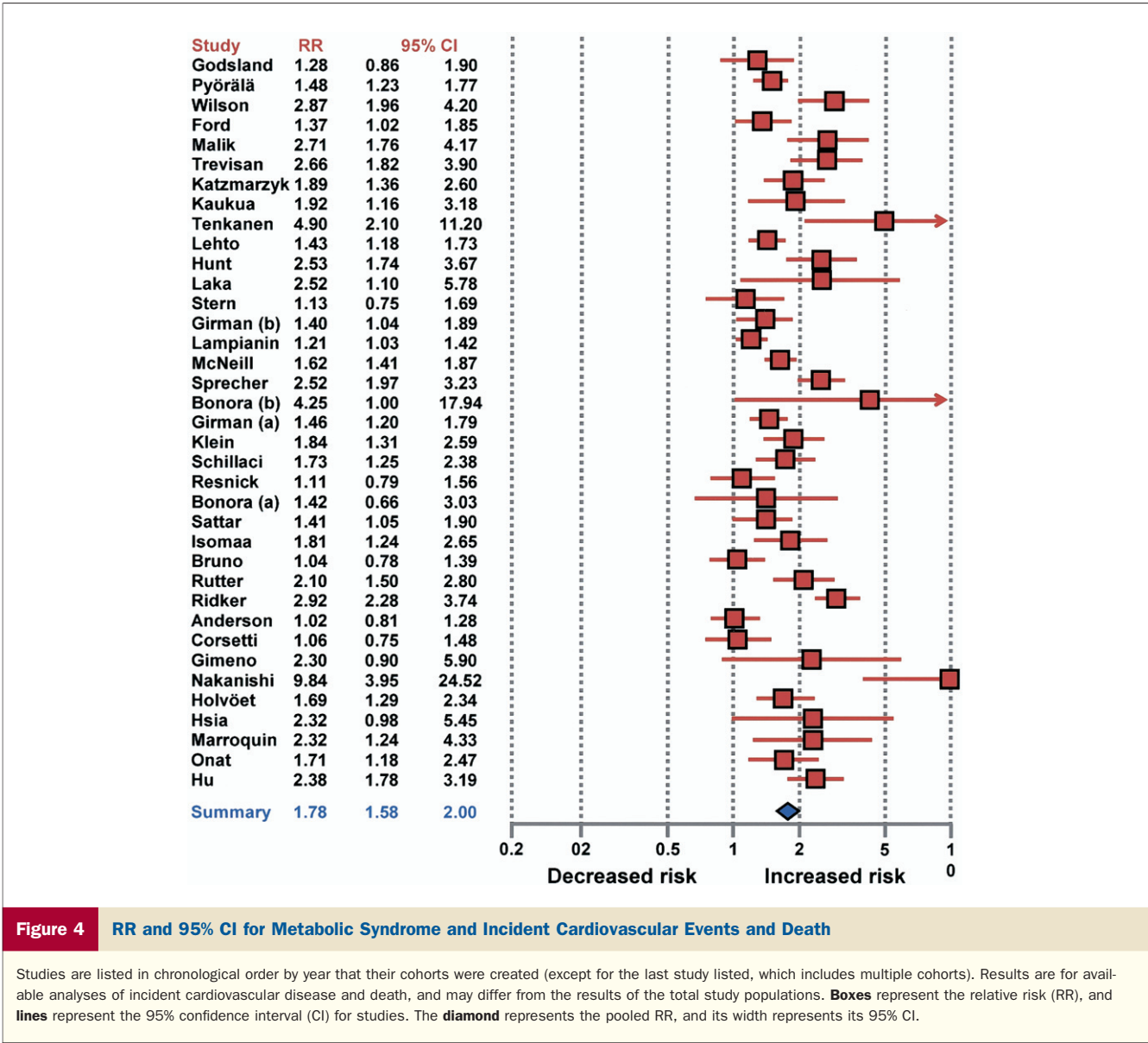


Figure 4 RR and 95% CI for Metabolic Syndrome and Incident Cardiovascular Events and Death

Studies are listed in chronological order by year that their cohorts were created (except for the last study listed, which includes multiple cohorts). Results are for available analyses of incident cardiovascular disease and death, and may differ from the results of the total study populations. **Boxes** represent the relative risk (RR), and **lines** represent the 95% confidence interval (CI) for studies. The **diamond** represents the pooled RR, and its width represents its 95% CI.

Sensitivity analyses. We performed 3 sensitivity analyses to test how robust the results of our meta-analysis were in relation to its design and assumptions.

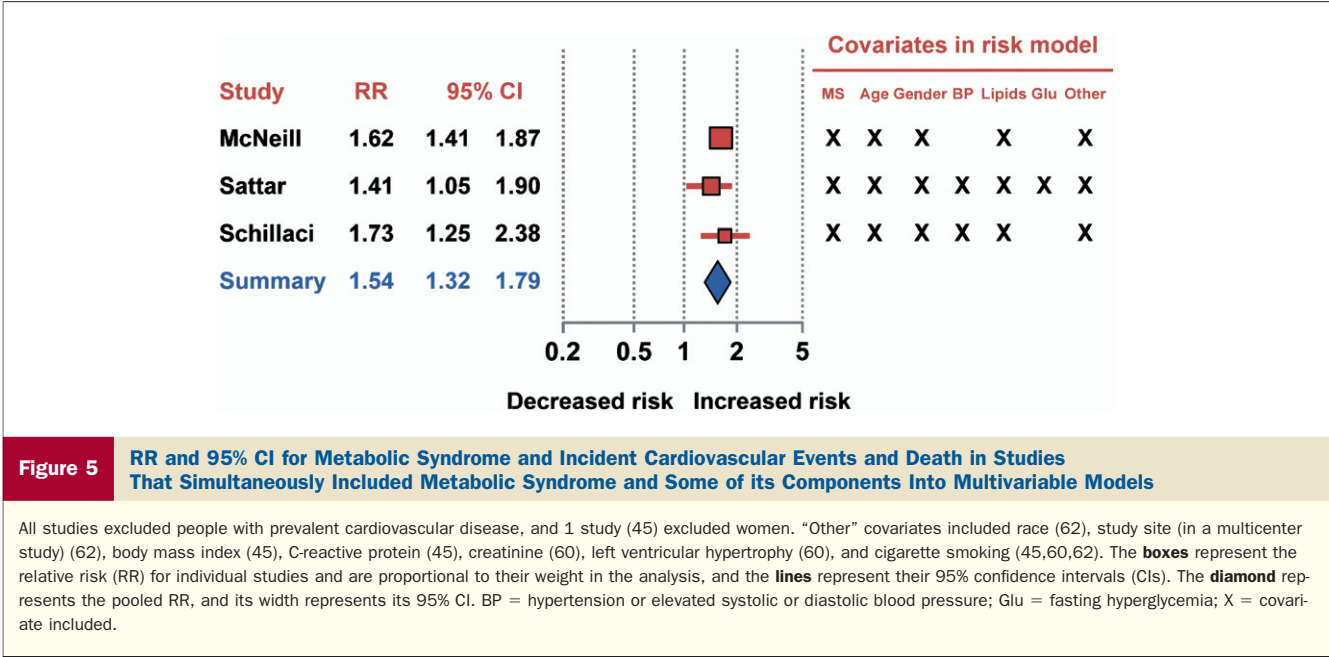
In the first, we included studies that had cohorts without prevalent cardiovascular disease and assessed incident coronary heart disease events (Fig. 6). After removal of 2 outliers (29,44), the pooled RR was 1.49 (95% CI 1.37 to 1.61), and there was no inconsistency (test of homogeneity $p = 0.8$; $I^2 = 0\%$). The first outlier (44) did not control for gender or smoking and had a very high loss-events ratio (161%), both of which introduce bias that could have increased its risk estimate. The other outlier (29) was designed as a study of risk factor clustering, rather than MetSyn per se, and thus the components and their thresholds were dissimilar from the other studies (e.g., it did not incorporate any measure of obesity).

In the second sensitivity analysis, we included only the 12 studies (listed earlier) that simultaneously limited selection,

detection, and attrition biases, since these are well recognized and important contributors to systematic error in observational studies. The results of this analysis were similar to those of the overall analysis (RR 1.58, 95% CI 1.34 to 1.87), with similar inconsistency across studies ($I^2 = 75\%$).

For the last sensitivity analysis, we re-analyzed the original data after excluding 1 study (28), which itself was a meta-analysis and potentially introduced error related to the unreported but possible heterogeneity of its included cohorts. Removing this study did not account for the underlying heterogeneity among studies ($I^2 = 81\%$) and did not change the general results (RR 1.83, 95% CI 1.62 to 2.07).

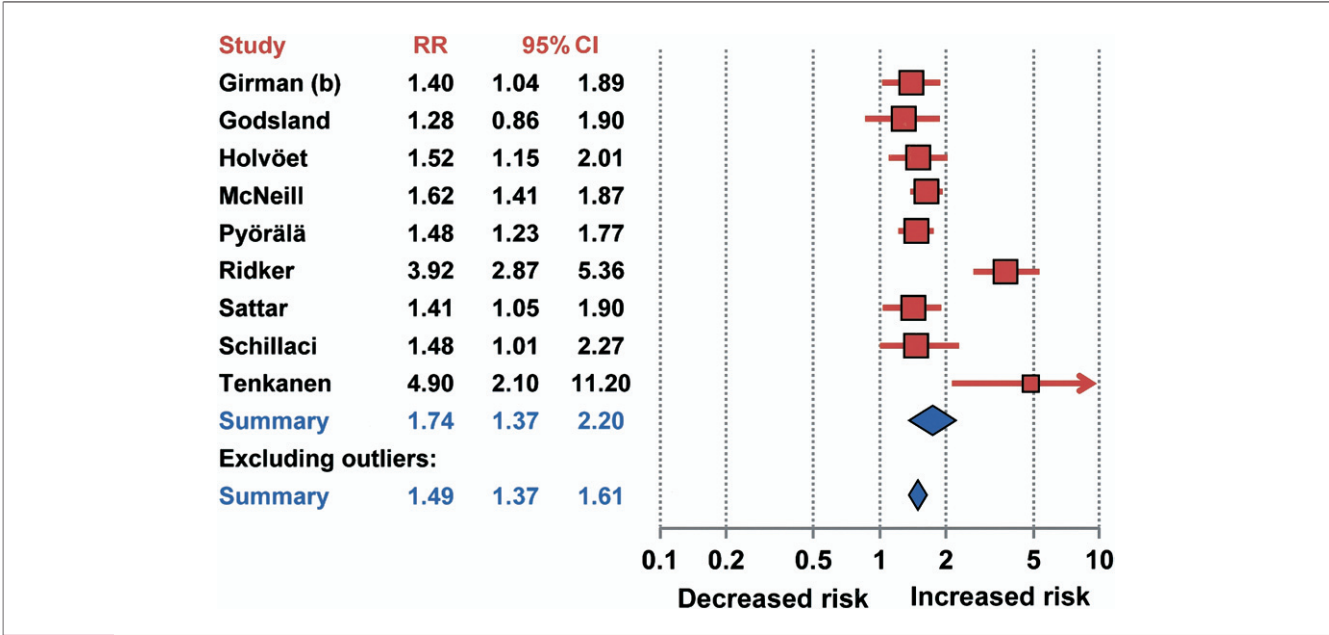
Publication bias. The funnel plot was asymmetric (Fig. 7, blue), suggesting small-study bias (either the absence of or inability to find studies with smaller or negative risk estimates) or unexplained heterogeneity. The fail-safe n for our pooled analysis is 3,846, which is reassuring since it is



very unlikely that there are over 100 unpublished or undiscovered studies for every 1 study we found. The trim-and-fill method imputed missing studies and recalculated our pooled risk estimate (Fig. 7, red). The imputed RR was 1.68 (95% CI 1.48 to 1.91), which is similar to our original risk estimate, suggesting that the apparent publication bias in this area is insufficient to affect our results or interpretations in a meaningful way.

Discussion

This study found that the current evidence, drawn from a large number of longitudinal studies that included 172,573 people, indicates a significantly increased risk of cardiovascular events and death in people with the MetSyn. The data demonstrate that the cardiovascular risk conferred by the MetSyn was a third higher in women than it was in men.



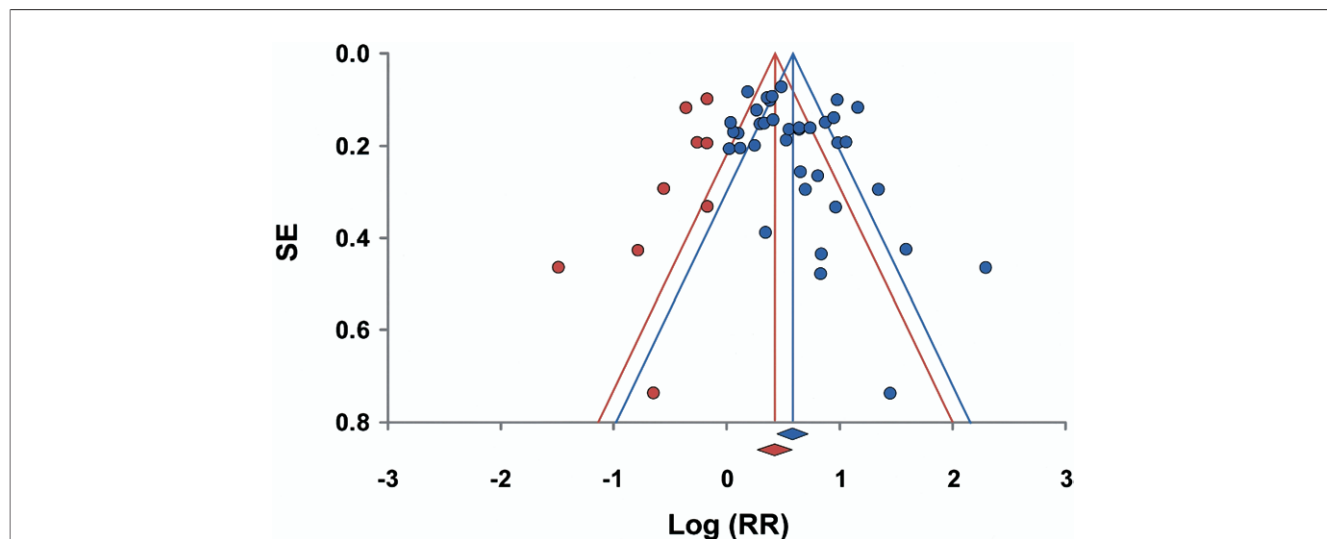


Figure 7 Publication Bias and Its Potential Impact

The **blue circles** represent individual studies, the **blue lines** are the funnel plot, and the **blue diamond** is the relative risk (RR) and 95% confidence interval for the meta-analysis. The **red circles** represent imputed studies, and the **red lines** represent the adjusted funnel plot. The **red diamond** is the RR and 95% confidence interval for the meta-analysis, after adjusting for publication bias. Log (RR) = logarithm of the RR; SE = standard error.

The best evidence came from the studies in which people without coronary heart disease were followed for incident coronary heart disease events, which except for 2 outlying studies showed a slightly attenuated but similar and highly homogeneous risk compared with the overall analysis. The most compelling evidence comes from our pooled analysis of studies that simultaneously adjusted in multivariable models for both MetSyn and its components. The analysis of these methodologically rigorous and statistically homogeneous studies demonstrates that the MetSyn confers cardiovascular risk beyond that which is associated with its component risk factors.

Our findings may shed light on important methodologic issues that created difficulty in making strong inferences from previous studies' results. We found that many of these cohort studies were methodologically limited by a high degree of attrition bias. Subjects who were originally enrolled but then were lost to follow-up can affect the risk estimate, especially if the numbers lost are a large proportion of (or in some of the studies we included, multiples of) the number of outcome events. We found that this attrition bias was a significant source of variability in study results and markedly overestimated the cardiovascular risk associated with the MetSyn, while studies that limited this bias had a pooled risk similar to that of the overall analysis.

The data reveal that definitions of MetSyn based on factor analysis were far more predictive of cardiovascular events and death than were other definitions. Since factors are created by integrating highly correlated risk factors in the specific population being studied, this may be expected. It should be recognized, however, that factors are statistical phenomena that cannot be applied readily to clinical prac-

tice. Our findings show that the WHO-based criteria were better than NCEP-based criteria in predicting cardiovascular events and death, and that the substitution of body mass index for waist circumference or waist-to-hip ratio in these criteria did not appear to affect their robustness.

Limitations of our review include the inherent assumptions of meta-analysis. Since individual patient data were unavailable, we used aggregate data as reported in published articles (or as provided by their authors). This commonly used approach may not detect and cannot solve methodologic problems affecting the primary studies. Also, our interpretations of between-study subgroup analyses may be less valid than within-study subgroup analyses, and there is a risk of type I error due to multiple testing in our analyses. The strengths of our review include its exhaustive search strategy, which likely captured most relevant studies. Also, the success in procuring data from most study authors overcame the lack of key data in published reports. The principal strengths of our study are the fundamental strengths of meta-analysis, which overcome selective and potentially biased inclusion and weighing of articles' results when interpreting the evidence, which can occur with narrative reviews.

Our findings are applicable to clinical practice. Only few of the studies in our analysis were published before development of the 2003 NCEP guidelines designed to aid clinicians in recognizing and targeting MetSyn. Whether the association between MetSyn and cardiovascular risk is sufficient to support aggressive intervention for these patients was subject of debate, but the strength of the evidence about the association is now even clearer. Clinicians can use this evidence as motivation when counseling patients. Of

note, our analyses neither support nor refute the role of insulin resistance or any other mechanism as mediators of the observed association between MetSyn and cardiovascular risk. Furthermore, our analyses do not yield therapeutic inferences.

These studies were conducted in diverse populations, including many rural and urban regions of the U.S., Norway, Sweden, Finland, the Netherlands, Scotland, England, Spain, Italy, Poland, Turkey, and Japan. People in developing countries, where obesity and its comorbidities are becoming more prevalent, are underrepresented in the current data. Only 1 original article included in our study used criteria apparently modified to account for different ethnic characteristics (58). The 2005 International Diabetes Federation Consensus (63), which provides a “worldwide” definition of the MetSyn that applies different measures of obesity for different ethnicities, should be incorporated in future research. Also requiring further study are children and young adults, in whom identification of MetSyn may have the greatest impact on public health if it leads to successful interventions to prevent cardiovascular disease.

Given the cumulative results of these studies, investigators should design and conduct large randomized trials of aggressive dietary, lifestyle, and pharmacologic interventions in people with MetSyn. Our findings suggest that in addition to targeting individual cardiovascular risk factors, primary prevention trials should study interventions that address the MetSyn as 1 entity.

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